UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,139	12/17/2002	Anne Eckert	ST99042USPCT	1457

5487 7590 01/14/2008

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

Office Action Summary	Application No.	Applicant(s)	
	10/088,139	ECKERT ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of May 7, 2007 on November 6, 2007. Claims 6-8 are amended. Claims 9-25 are new.

Claims 1-25 are under consideration.

Withdrawn Rejection

35 U.S.C. § 112, 2nd parag.

Applicant's arguments, see amendment to the claims, filed November 6, 2007, with respect to the rejection of claim 8 for reciting "said cell" of claims 1-5. Claims 1-5 had no recitation of any cell. Applicant's amendment to claims 8, amending "said cell" to "a cell" have been fully considered and are persuasive. The rejection of claim 8 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 remain rejected and new claims 9-25 are newly rejected under 35 U.S.C. 101 the claimed invention lacks patentable utility, for reasons of record, July 14, 2005, April 4, 2006, and May 7, 2007.

Applicant's arguments filed November 6, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the Office Action at page 4, last 3 lines: "the specification and the art provide no guidance what relationship multimutated PSI, apoptotic T lymphocytes and Alzheimer's disease have to do with each other such that the claimed non-human mammals can be used." Applicant indicates that the Office Action's requirement is improper with respect to the utility requirement. 35 USC § 101 recites "any new and useful" and that the specification, pages 5-7, asserts the use of the claimed animal and that it is a model of AD. Applicant indicates that "any use" should be as Applicant perceives (Applicant's response, pages 5-6). In response, this is not persuasive. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

While Applicant refers to the specification that indicates that the claimed animals are models of Alzheimer's disease, nothing in the art indicates that any of the characteristics exhibited by the mice (apoptotic lymphocytes and reduced SOD activity and reduced glutathoine reductase activity in the brain) are symptoms of Alzheimer's disease. It is noted at this point that the art teaches that Alzheimer's patients exhibit an increase in SOD and glutathione reductase activity. This phenotype is opposite to that of the mice described in the specification, Example 8. For further discussion, see Enablement. The claimed animals lack substantial utility because further research is required in demonstrating that apoptotic lymphocytes and reduced SOD activity and reduced glutathione reductase activity in the brain are related to Alzheimer's disease. Subsequently, the use of the mice as a model of AD and its use in screen for treatment drugs is not readily apparent.

Applicant indicates that the animal model of the present invention permits, e.g. measurement in blood cells, a renewable tissue that is easily and relatively non-invasively obtained from an animal, for modeling effects on nervous tissues: tissues not so easily obtained and not renewable. Applicant indicates that one utility corresponds to "the phenomena of cell death in AD" (Applicant's response, page 6). In response, this is not persuasive. Blood cells are structurally and functionally not the same as neural cells and thus are not representative of neural cells. In addition to this, while the mice described in the specification exhibit apoptotic lymphocytes, it is not clear what disease or disorder apoptotic lymphocytes is a symptom of. As such, the use of the claimed animals as a model of apoptotic lymphocytes is not readily apparent.

Applicant indicates that the Examiner's reliance on the quote from Lilly is misapplied. "Utility" relates to "use" or how something is employed. Thus, what it does would seem an

important consideration for describing "utility". Applicant indicates that past patent applications merely disclosing ESTs clear described the composition of each compound (what it is), but because what each compound did was not adequately described, utility rejections were made (Applicant's emphasis, Applicant's response, page 6). In response, while the specification clearly indicates "what is" the phenotype of the claimed animals: apoptotic lymphocytes and reduced SOD activity and reduced glutathione reductase activity in the brain, neither the specification nor the art provide any guidance as to what relationship these phenotypes have with any disease. One could generally say that the animals are used in screens to identify drugs that treat their symptoms. However, it is unclear to an artisan why the symptoms would need to be treated if they are not a symptom of disease. The specification asserts that these phenotypes are characteristics of Alzheimer's disease (specification, pages 5-6), however, nothing in the art indicates that the characteristics exhibited by the mice described in the Examples of the specification are characteristics of Alzheimer's disease. In expanding the idea of whether the phenotypes are characteristics of other medical conditions such that the claimed animals can be used, the specification provides no specific guidance as to what these other medical conditions are. As such, indicating the phenotypes of the claimed animal is not necessarily sufficient for addressing specific and substantial utility. The claimed animal lacks specific utility because the specification's teaching of mutated presenilin and apoptotic lymphocytes and reduced SOD and glutathione reductase activity implies that the claimed mice is a model of an undisclosed disease. The claimed animal lacks substantial utility because further research is required to determine what this undisclosed disease is.

While Applicant indicates that the use does not have to be the one proposed by the Examiner and can be the one that the Applicant has asserted (Applicant's response, page 6), Applicant's assertion is not persuasive. Again, it is unclear what use apoptotic lymphocytes have. Applicant indicates that the apoptotic blood cells mirror those of CNS tissues and that obtaining blood cells is much easier than obtaining CNS biopsies. The blood cells have been modified (through modifying genetic makeup of the organism) to mirror apoptotic events of the CNS. As such, the genetic manipulation results in a model representative of cell death in AD (Applicant's response, page 7). In response, this is not persuasive. Blood cells are not representative of other cell types and the activity of one type of cell is not indicative that other cell types have the same activity. To illustrate this point further, the mice described in the specification exhibit apoptotic lymphocytes; however, nothing in the specification indicates that the neural tissue of the mice is apoptotic. Example 8 of the specification indicates that two enzymes were measured in the transgenic mice; however, this is not indicative that the mice exhibited apoptosis in their brains. As such, an assertion that a phenotype occurring in tissue that is not associated with Alzheimer's disease is not representative of Alzheimer's disease.

Applicant indicates that AD is not a claim element of claim 1 and the use satisfying a statutory utility does not have to be claimed (Applicant's response, page 7). In response, the Examiner was not requiring that "Alzheimer's disease" be put in claim 1. The rejection was that the specific and substantial use of the claimed animal was not readily apparent.

Applicant indicates that the Office Action stating on pages 12-13, "(t)he rejection is maintained because neither the specification nor the art provide any guidance that the claimed animals are a model of Alzheimer's disease," is baseless. Applicant indicates the excerpts from

the specification, pages 5-7. In response, while the specification asserts that the claimed animals are models of Alzheimer's disease, asserting that the mice are models is not the same as demonstrating that they are, as illustrated by Applicant's Examples. The Examples in the specification teach that the mice comprising a transgene construct encoding mutated presenilin exhibit apoptotic lymphocytes and reduced activity of SOD and glutathinone reductase. Nothing in the art teaches that these are characteristics of Alzheimer's disease. As such, the asserted utility that the claimed animals are models of Alzheimer's disease is not persuasive in overcoming the rejection.

With regard to Applicant responding to the Office Action, page 8, line 12, "it is unclear whether PS1 comprising 5 mutations triggered apoptosis in the claimed animals," Applicant indicates that the statement is irrelevant. Applicant indicates that pedantic argument of what "triggers" versus what facilitates is not productive. Clearly cells with multimutated PS1 survive to produce multiple copies. Whether the multimutated PS1 is said to "trigger" or merely results in "increased sensitivity to apoptosis" (specification, page 6, line 20) is a distinction not relevant to the rejection at hand (Applicant's response, pages 7-8). In response, the Examiner used the word "trigger" to indicate that the presence of the protein was necessarily the reason for the phenotypes exhibited by the claimed animals. Note that in the Enablement rejection, the art raises issues regarding phenotypes that occur non-specifically in transgenic animals (Office Action, May 7, 2007, page 14-15). As such, because the art does not teach a relationship between presenilin, apoptotic lymphocytes and reduction in SOD and glutathione reductase activity, the Examiner questioned if these phenotypes were the result of a non-specific effect.

Applicant wishes to clarify that while the discussion raised by the Examiner relates to neurodegenerative disease, the cells of the animals of the present invention also exhibit oxidative stress as manifest in the brains of the animals (specification, Example 8). Oxidative stress in brain tissue is another disease trait associated with neurodegenerative disease such as AD (Applicant's response, page 8). In response, as discussed above, and in the Enablement, decreased SOD and glutathione activity are not characteristics of AD.

With regard to the Office Action, page 8, lines 13-14, indicating, "it is unclear what pathology the claimed animals exhibit such that they are models of T-lymphocyte apoptosis in Alzheimer's disease," Applicant's indicate that this is a false requirement. Applicant indicates that the renewable cells are cells that can be biopsied to assess condition. The model is not one of T lymphocyte behavior, rather renewable cells, such as T lymphocytes are chosen as models to monitor other activities such as brain cells that may not be so available (Applicant's response, page 8). In response, as discussed above, lymphocytes are not models of brain cells. As such, this asserted use is not persuasive.

With regard to the Office Action, pages 8-10, wherein the Office Action asserts a requirement that a specific direct correlation to amyloid plaques be shown, Applicant indicates that this requirement has no sound legal basis. Apoptosis is associated with AD. See citation to Chui, specification, page 2. Thus, an association of the model to apoptosis in AD is shown. Metabolism of free radicals, a component of oxidative stress, is shown to be inhibited as expected in the brains of multimutated animals of the invention (Applicant's response, page 8). In response, since no copy of Chui was provided, the Examiner cannot comment on the publication. Nonetheless, while Applicant refers to Chui who indicate that transgenic mouse

models exhibit apoptosis without exhibiting any plaque formation, it is noted that nothing in the specification indicates that the claimed animals exhibit apoptosis in the brain. Example 8 indicates that there is a reduction in SOD and glutathione reductase activity; however, this is not indicative of Alzheimer's disease and is not indicative that the cells in the brain of the claimed animals were apoptotic.

In response to the Office Action, page 10 discussing that definitive diagnosis requires observation of neuritic plaques, Applicant indicates that if Alzheimer's disease were only manifest after death, there would be little concern. The lesson is that other symptoms are associated with AD and deterioration or amelioration of these symptoms can be observed before death (Applicant's response, page 8). In response, the only phenotype that can be seen while the claimed animals are alive is apoptotic lymphocytes. (It is noted that to measure SOD and glutathione activity in the brain, the animals would need to be sacrificed (specification, pages 19-20).) As discussed above, since the art does not provide guidance that apoptotic lymphocytes are a symptom of Alzheimer's disease, monitoring apoptotic activity of lymphocytes in the claimed mice is not readily apparent as an indicator of Alzheimer's disease progression.

Applicant indicates evidence of nexus between AD and cells having mutated presenilin is found on page 2, first parag. of the specification, and that mutations in this gene are associated with plaques and with other characteristics *inter alia* apoptosis and oxidative stress. Thus, mutated renewable cells evidencing such correlated characteristics are useful as surrogates for other cells in the organism, so as to avoid a need to sacrifice animals to study pathology (Applicant's response, page 9). In response, lymphocytes are not models of neurons and thus, it cannot be extrapolated that apoptotic lymphocytes are models of Alzheimer's disease.

Thus, the claims remain rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 remain rejected and new claims 9-25 are newly rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record, July 14, 2005, April 4, 2006, and May 7, 2007.

Claims 1-8 remain rejected and new claims 9-25 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record, July 14, 2005, April 4, 2006, and May 7, 2007.

Applicant's arguments filed November 6, 2007 have been fully considered but they are not persuasive.

Applicant indicates that the animals of the present invention demonstrate cellular impairments which are found in Alzheimer's disease and, in particular, exhibit increased sensitivity to apoptosis. There is no undue experimentation that is required to use the animals as claimed as for allowing an apoptotic phenomenon to be detected in renewable peripheral tissue

(specification, page 6, 2nd parag.) (Applicant's response, page 9). In response, the transgenic mice described in the specification exhibit apoptosis in their lymphocytes. As indicated above, it is unclear what symptom of disease apoptotic lymphocytes is. Applicant, above, has indicated that the apoptotic lymphocytes can be a model for apoptosis for neuronal cells seen in neurodegeneration. However, that is not persuasive because lymphocytes are not models of neuronal cells. As such, it would be undue experimentation for an artisan to determine the use of the claimed non-human animals that exhibit apoptotic lymphocytes. Neither the art nor the specification indicate what use an apoptotic lymphocyte, obtained from a transgenic animal overexpression a multimutated presenilin, has.

Applicant indicates that the mice in the specification have been shown to possess mutations associated with a neurodegenerative disease in humans and that these mutations results in measurable events also known to be associated with neurodegenerative disease. The mutations known to be associated with characteristics such as apoptosis in neurodegenerative disease are also shown to be associated with apoptosis in T lymphocytes of the same animals with the human FAD associated neurodegenerative disease. Thus, the mouse or other animal of the instant invention is clearly a model for characteristics of the neurodegenerative disease found in humans (Applicant's response, page 10). In response, as indicated above, apoptotic T-lymphocytes are not models of apoptosis seen in neural tissue.

Applicant provides a response regarding the Office Action's indication that the mutated form of PS1 behaves in a different manner than that of the wild type. Applicant indicates that this is not at all surprising since the mutation PS1 is associated with AD. The mutated and wild type protein are therefore expected to have different characteristics. Applicant indicates that

with regard to the Office Action indicating that, "it is unclear what biological activity (if any) PS1M5 has, such that apoptosis occurs in T lymphocytes," that the present invention does not require complete understanding of the mechanism of action. The Figures demonstrate that the mutation associated with Alzheimer's produces a measurable effect that can be used to monitor characteristics associated with neurodegenerative diseases such as AD in renewable tissues such as T lymphocytes. In response, the Examiner addressed the issue of PS1M5 having severe structural alterations to indicate that PS1M5 was likely to behave unexpectedly and result in phenotypes that are unexpected and unrelated to Alzheimer's disease (Office Action, May 7, 2007, page 13). Subsequently, the possibility is raised that some of the phenotypes exhibited by the claimed animals are unrelated to any disease or disorder.

With regard to page 13 of the specification relying on disbelief of an evidentiary document, Applicant indicates that a declaration was filed wherein Applicant declared that they each believe the statements of the specification to be true and that penalties under 18 US § 1001 are specifically acknowledged (Applicant's response, pages 10-11). In response, indicating that apoptotic lymphocytes in transgenic animals that express a multimutated form of presenilin are a model of Alzheimer's disease does not indicate to an artisan how to use the claimed animal. Lymphocytes are not models of neurons and apoptotic lymphocytes are not a symptom found in Alzheimer's disease. As such, to indicate how apoptotic lymphocytes related to Alzheimer's disease requires undue experimentation as nothing in the art indicates this relationship.

With regard to the Office Action indicating, "according to the art, an artisan cannot reasonably predict that the components necessarily work in various species of animals" (emphasis added), Applicant indicates that the wrong standard is used. The standard for

enablement is whether undue experimentation is required, not certainty of outcome. The Office Action presents no evidence that reference articles cited in this rejection teach or suggest in any way that undue experimentation would be required to practice the invention. Similarly, many promoters are known in the art. Skilled artisans are capable of selecting one or more promoters and routinely practice using multiple promoters in order to optimize output for the intended purpose (Applicant's response, page 11). In response, the rejection with regard to unpredictability of transgene constructs in transgenic animals (Office Action, July 14, 2005, page 8) was made because no guidance was given regarding how to predictably arrive at non-human mammals that express a multimutated form of PS1, wherein said non-human mammal exhibits apoptosis in renewable peripheral tissue. Rather, to make the wide variety of mammalian species and transgene constructs such that a particular phenotype is exhibited is undue experimentation, as the art teaches that there is unpredictability in arriving at the appropriate combinations of transgene and species of host mammal. With regard to the issue of the promoter, Cowan et al. was used to illustrate one component of the transgene construct, the promoters, do not behave predictably in different species of mammals. Since the claims encompass a wide variety of transgenic host mammalian species and a wide variety of promoters from different species of animals, it would be undue experimentation to find the appropriate set of transgene constructs for each mammal encompassed by the claims such that the claimed invention could be practiced.

With regard to the Office Action indicating, "it is unclear that the mice described in the specification necessarily exhibit apoptotic lymphocytes because of the transgene or because of unrelated factors (e.g. genetic background and/or the PS1M5 inducing non-specific biological activity) which result in mice that exhibit this particular phenotype," Applicant indicates that this

issue is irrelevant. Applicant indicates that "(p)henotypic activity matches that known to be associated with the mutated gene in humans." (Applicant's response, page 12). In response, it is not entirely clear what is meant by, "(p)henotypic activity matches that known to be associated with the mutated gene in humans." If Applicant is indicating that the phenotype in the mice is the same as that in humans, then Applicant's response is not persuasive. A search in the art has not indicated that there is a relationship between presenilin, apoptotic lymphocytes and Alzheimer's disease. Because the art does not teach this relationship, the question was raised as to whether the apoptotic lymphocyte phenotype was a result of a non-specific effect such as genetic background (Auerbach publication, Office Action, May 7, 2007, page 14). With regard to the claimed mice exhibiting a reduction in superoxide dismutase (SOD) and glutathione reductase activity (specification, Example 8), the art teaches that these are characteristics opposite to that exhibited by Alzheimer's patients. Delibas et al., 2002, Clinical Biochemistry, 32: 137-141 teach that SOD levels were increased in Alzheimer's patients (Delibas, et al., abstract, under "Results"). Lovell et al., 2000, Free Radical Biology and Medicine, 28: 418-427 teach that increased levels of glutathione reductase and superoxide dismutase are seen in the AD brain (Lovell et al., page 422, 2nd col.).

Applicant indicates that no undue experimentation is apparent with regard to the issue of phenotypes occurring because of unrelated factors such as genetic background or PS1M5 inducing non-specific biological activity. Certainty is not a requirement of patent law or even science. Pedantic argument whether something "necessarily exhibits," "most likely exhibits," "probably exhibits" is not necessary to decide the issue of whether undue experimentation is required to practice the claimed invention (Applicant's response, page 12). In response, it is

undue experimentation to make the wide variety of transgenic non-human mammals and transgene constructs encompassed by the claims, wherein the non-human mammal exhibits a particular phenotype (here, apoptotic lymphocytes). Auerbach was used to illustrate that genetic backgrounds in the various different mammals encompassed by the claims can result in unexpected phenotypes. Thus, an artisan would be required to make a wide variety of transgenic non-human mammals comprising transgene constructs that express a multimutated PS1, wherein said non-human mammal exhibits apoptotic lymphocytes, in order to identify which combination of transgene construct and mammalian specie would result in apoptotic lymphocytes. This is undue experimentation.

With regard to the Office Action indicating, "the specification does not teach how to arrive at apoptosis in other renewable peripheral tissue such as blood," Applicant indicates that the rejection appears based on a faulty assessment of the skilled artisan. T lymphocytes are a blood cell. The skilled artisan would also be aware that some components of blood such as red blood cells and platelets do not have nuclei and therefore cannot initiate apoptosis. Other blood cells such as B lymphocytes share the same stem cells, erythropoietic stem cells as T lymphocytes. The chemical anecdote of the Office Action cannot be considered instructive in the present situation. In response, the issue at hand was that the claims are broad for a wide variety of renewable tissues. In blood, as pointed out by Applicant, this includes B lymphocytes. The specification only teaches that T lymphocytes are apoptotic; the specification does not teach that other renewable tissues, encompassed by the claims, are enabled. It is noted that in the Office Action of July 14, 2005, page 12, other renewable tissues include spleen, liver, skin, and lining of the intestine. Nothing in the specification teaches that the claims could be practiced for

the wide breadth of "renewable tissues" as encompassed by the claims. Applicant indicated with response to this rejection that non-operative embodiments are permitted (Applicant's response, October 3, 2006, page 5). The Examiner indicated case law of In re Soll, In re Fisher, In re Wright, In re Vaeck, and In re Dreshfield to indicate that if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Such is the case in regards to the instant claims as written. The claims encompass a wide variety of "renewable tissues"; however, the number of inoperative combinations is large (i.e. the specification does not disclose that other renewable tissues undergo apoptosis) and thus, this requires one of ordinary skill in the art to experiment unduly in order to practice the claimed invention.

Applicant indicates that similar properties were shown in brain cells, cells quite different for the T lymphocytes. These major differences are illustrative that the characteristics observed from the mutated T lymphocytes are not specific to the lymphocytes but are found in a variety of the cells. Undue experimentation would not be involved for selecting and testing cells for the desired phenotypic expression. In response, with regard to Applicant indicating that "similar properties were shown in brain cells," the Examiner has gone through the specification and found that the only teaching of phenotype regarding brain cells was in Example 8. Example 8 indicates the decreased activity of SOD and glutathione reductase; however, this is not indicative that apoptosis occurred in the brains of the transgenic mice. With regard to the mice exhibiting increased lipid peroxidation, the multimutant transgenic mice exhibit levels similar to that of wild type, i.e. not statistically significant, as evidenced by the error bars (specification, Figure

11C). Applicant indicates that major differences are illustrative that the characteristics observed from the mutated T lymphocytes are not specific to the lymphocytes but are found in a variety of the cells. However, in looking through the specification, nothing in the specification teaches that other cell types were examined and exhibited any apoptosis. As such, the specification does not provide guidance for the full breadth of "renewable tissues."

With regard to the paragraph bridging pages 17 and 18 of the Office Action, Applicant indicates that the Office Action attempts to support the rejection by opening the discussion with neurodegenerative diseases and then switches the discussion to Alzheimer's disease. The Office Action indicates that "the specification does not provide guidance that the protein recapitulates symptoms associated with the disease such as neuritic plaques." Applicant indicates that this rejection is improper. Applicant indicates that the specification provides guidance showing relevance relative to Alzheimer's disease (specification, Example 8). Metabolism of free radicals, apoptosis, and Ca^{++} mobilization are associated with the transgenic animals and Alzheimer's disease. Applicant indicates that at least this portion of the specification shows that the mutated protein has relevance to "symptoms associated with the disease such as neuritic plaques." While neuritic plaques are not shown, other symptoms related to Alzheimer's disease is shown (Applicant's response, page 13). In response, as discussed above, the brain phenotypes described in Example 8 are not indicative that the mice have any symptoms of Alzheimer's disease. With regard to the apoptotic lymphocytes, nothing in the art teaches that Alzheimer's patients exhibit apoptotic lymphocytes. As such, the use of the mice with regard to apoptotic lymphocytes to treat Alzheimer's disease is not readily apparent.

In Applicant's Closing Remarks, Applicant indicates that the specification teaches how to make the transgenic animal expressing a multimutated PS1. Examples show that apoptosis and other Alzheimer's disease related phenomena are measureable in peripheral tissue. No undue experimentation is required (Applicant's response, page 13). In response, while the specification indicates particular phenotypes of the transgenic mice comprising multimutated preseniilin, none of the brain phenotypes relate to Alzheimer's disease. With regard to the apoptotic lymphocytes, nothing in the art indicates that this phenotype is related to Alzheimer's disease. As such, the use of the mice for any of these phenotypes is not readily apparent. Applicant indicates that the claims do not recite measuring plaques as the Examiner wishes to require. However, the invention is a model useful for monitoring effects of exogenous compounds on symptoms related to Alzheimer's disease. The model allows easy monitoring of some symptoms because renewable tissues such as blood can be repeatably measured as desired. This model was designed specifically to avoid the need to analyze the animals for necropsy (Applicant's response, page 14). In response, while Applicant indicates that the lymphocytes can be used as a model for Alzheimer's disease, an artisan cannot use apoptotic lymphocytes as a model of Alzheimer's disease because a) the art does not teach that apoptotic lymphocytes are a symptom of Alzheimer's disease and b) lymphocytes are not models of neurons.

Thus, the rejections remain.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7 remain rejected and new claims 13-16, 21 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed November 6, 2007 have been fully considered but they are not persuasive. Claims 1-5, 7 were rejected as each sentence of the claims were missing articles, "a," "an," or "the." No amendment was made to the claim and no response was provided regarding this issue. As such, the rejection regarding this issue remains. Claims 13-16, 21 are included in the rejection as they depend on claims 1-5, 7.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Joanne Hama
Art Unit 1632

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633